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Bromide selective fluorescent anion receptor with glycoluril molecular scaffold

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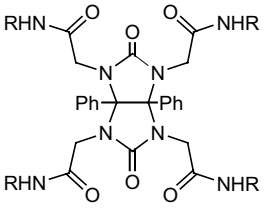
Abstract—Glycoluril based fluorescent anion receptor has been designed and synthesized. Anion binding studies carried out using fluorescence spectroscopy and ^{1}H NMR revealed that this compound displays good affinities for bromide ion.

Artificial receptors for selective anion recognition is an area of intensive investigation as anions play a fundamental role in a wide range of chemical and biological process.[1] However, fluorogenic or chromogenic sensors for selective detection of anions are much less explored despite the fact that many examples of anion receptors or cation sensors have been reported.[2] For sensing approach, anion recognition site is usually coupled to the reporting groups, which binding process is transduced into a signaling event. Anion complexation induces changes in the spectroscopic properties of host molecules, leading to guest anion specific color change or fluorescent emission spectrum.

Recently, we introduced a diphenyl glycoluril moiety into the framework of hosts and produced host molecule **1** capable of binding anions by the cooperative action of multiple amide hydrogen bonds.[3] The anion receptor **1** binds with spherically shaped halide ion in 1:1 stoichiometry and has a high affinity for fluoride ion. Four amide N–H hydrogens attached at the corner of glycoluril form a cavity and point to the anion located at the center of the concave structure of glycoluril. In these studies, mainly guest-induced ^{1}H NMR shifts were used to determine the association constants. However, ^{1}H NMR titration method is limited when the host and guest associate strongly.[4] This limitation can be overcome by the incorporation of fluorescent chromophores into the host due to their high sensitivity and low detection limit.[5] Therefore, to enlarge the scope of the receptor **1** as a fluorescent sensor, we designed fluorescent receptor **2**, which has fluorescent naphthalene moieties instead of the phenyl groups. Here we would like to report the binding properties of receptor **2** with various anions (Fig. 1).

The new naphthalene receptor **2** was synthesized in 70% yield from the reaction of tetraacylchloride **3**[3b] and 2-naphthaleneamine. The compound **2** was characterized by ^{1}H NMR, ^{13}C NMR, and high resolution mass spectrum.[6]

The naphthalene receptor **2** displayed strong fluorescence emission in acetonitrile as shown in Figure 2. The excitation and emission wavelength were 242 and 350 nm, respectively. The relative quantum yield of receptor **2** was investigated by comparing the ratio of the fluorescence emission intensity maximum to



1 R= 4-nitrophenyl

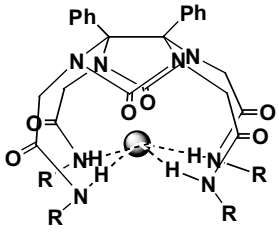


Figure 1. The structure of receptor **1** and the proposed binding mode with halide ion.

Keywords: Anion receptor; Glycoluril.
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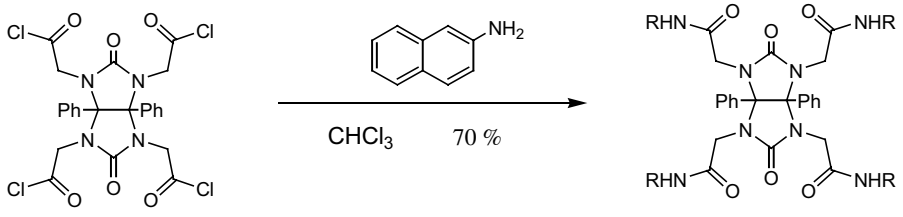

3 **2** R= 2-naphthalene

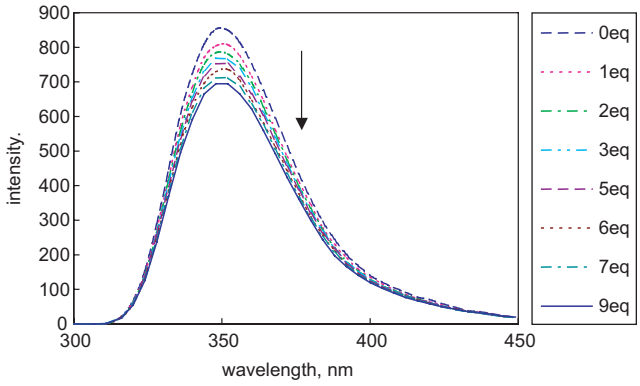

Figure 2. The change of fluorescence spectra in the receptor **2** when tetrabutylammonium bromide was added.

UV–vis absorbance at excitation wavelength used for the sample with that of standard.[7] 9,10-Diphenylanthracene ($\Phi = 0.96$) was used as fluorescence standard.[8] The quantum yield of receptor **2** was determined to be 0.12. The associations between the naphthalene receptor **2** and spherically shaped halides were investigated by fluorescence titration. The fluorescence change of the receptor **2** was monitored in acetonitrile. The intensity of emission spectrum from 10 μM solution of the naphthalene receptor **2** decreased as the concentration of tetrabutylammonium halides salts was increased, which indicates the association between the receptor **2** and halides. The plot of F^0/F versus the concentration of halides gave a straight line as shown in Figure 3. The linearity of Stern–Volmer plot further confirms the formation of one type complex between receptor **2** and halide. The stoichiometry between host and guest was determined by fluorescence Job plot, which showed evident 1:1 stoichiometry (Fig. 4).[9] A Benesi–Hildebrand plot[10]

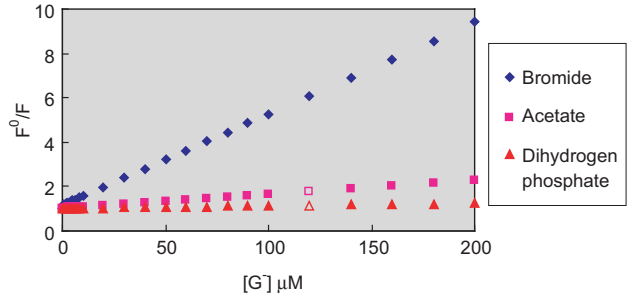

Figure 3. The Stern–Volmer plot for the association of receptor **2** and various anions.

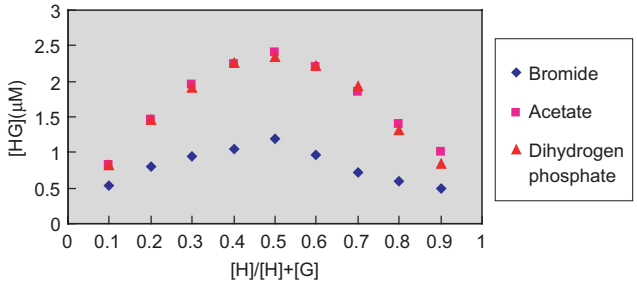

Figure 4. Job plot between receptor **2** and various anions. The complex concentration, [HG] was calculated by the equation[9] $[HG] = \Delta F/F^0 \times [H]$.

by use of change in the 350 nm fluorescence intensity gave association constants. The results are summarized in Table 1. From the experiments, the receptor **2** showed the highest association constant $1.2 \times 10^5 \pm 1.4 \times 10^4$ for bromide. The order of association constants was $Br^- > Cl^- > F^- > I^-$.

The complexation abilities of receptor **2** to the halides were also measured by standard ^1H NMR titration experiments in DMSO-d_6 using a constant host concentration (2 mM) and increasing concentrations of anions (1–10 equiv). The chemical shift data were analyzed by EQNMR.[11] The addition of tetrabutylammonium halide salts to the solution of **2** in DMSO-d_6 resulted in downfield shifts in both the amide N–H hydrogen and CH_2 hydrogens next to amides. Therefore, the signals of amide N–H or the signals of CH_2 protons located next to amide groups were used to determine the association constants for receptor **2** and halides. Whichever

Table 1. Association constants (M^{-1}) of receptor **2** with tetrabutylammonium anions in acetonitrile from fluorescence titration

Anion	Association constants (K_a)
F^-	$1.4 \times 10^4 \pm 8.0 \times 10^2$ (14[b])
Cl^-	$2.4 \times 10^4 \pm 2.8 \times 10^3$ (34[a])
Br^-	$1.2 \times 10^5 \pm 1.4 \times 10^4$ (2.8×10^2[a])
I^-	$1.3 \times 10^4 \pm 5.3 \times 10^2$ (7.6[a])
$CH_3CO_2^-$	$1.2 \times 10^4 \pm 1.8 \times 10^2$
$C_6H_5CO_2^-$	$9.6 \times 10^3 \pm 10$
$H_2PO_4^-$	$7.5 \times 10^4 \pm 9.5 \times 10^2$

The numbers in parentheses are association constants in DMSO-d_6 from ^1H NMR titration.

[a] Errors in K_a are estimated to be less than 10%.

[b] Errors in K_a are estimated to be less than 20%.

peaks were chosen, binding constants between the receptor **2** and anions showed similar values. From the ^{1}H NMR experiments in DMSO-d_6, the receptor **2** showed the highest affinity again for bromide. The amide peak in the receptor **2** without bromide appeared at 10.178 ppm in DMSO-d_6. The addition of tetrabutylammonium bromide to the solution of **2** leads downfield shifts of amide N–H peak. The amide peaks moved to until 10.188 ppm with 5 equiv of bromide. No further shifts were observed. The association constants calculated from ^{1}H NMR titration gave $2.8 \times 10^2\,M^{-1}$ for bromide. The association constants for the other halides calculated from ^{1}H NMR titration are also summarized in Table 1.

The preference for bromide suggests that the cavity formed by four amide bonds is more complementary to the size of the bromide ion than to the size of other halide ion. As anions have diverse geometries, complementarity between the receptor and anion is crucial in determining selectivity.[1b] The complementarity between the receptor and halides is mostly achieved by the size of the receptor binding site due to the spherical shape of halides. Unless the binding site is quite rigid for the size of a particular halide, halide anions tend to associate with receptors according to their basicity[12] (i.e., in the order of $F^- > Cl^- > Br^- > I^-$). However, many examples of size discrimination of halides due to the size of receptor binding site have been reported. In these cases, a better fit dominates the expected higher hydrogen bonding affinity of the hard fluoride for the hard hydrogens.[13] We propose that four naphthalenes in receptor **2** would form a larger cavity than the cavity formed from four benzenes in receptor **1** as naphthalene is larger than benzene.

Therefore, the cavity in receptor **2** fits well with the size of bromide while the size of cavity in receptor **1** fits with the size of fluoride.

We also investigated the binding of carboxylate and dihydrogen phosphate with receptor **2** with fluorescence titration. The linearity of Stern–Volmer plot confirms the formation of complex between receptor **2** and these anions (Fig. 3) The Job plot of both carboxylate and dihydrogen phosphate for the receptor **2** in acetonitrile showed 1:1 binding stoichiometry (Fig. 4).[14] The calculated association constants of acetate and benzoate were $1.2 \times 10^4 \pm 1.8 \times 10^2$ and $9.6 \times 10^3 \pm 10\,M^{-1}$, respectively. In the case of $H_2PO_4^-$, the association constant was calculated as $7.5 \times 10^4 \pm 9.5 \times 10^2$. The receptor **1** binds with carboxylate 1:2 stoichiometry and dihydrogen phosphate in mixed stoichiometry. The binding mode of these anions has been reported previously, which two amide arms in one side of glycoluril binds with one anion.[3b] Probably, the cavity formed with four amide hydrogens in receptor **1** is not large enough to accommodate these anions while cavity formed with two amide hydrogens is large enough to accommodate these anions. In receptor **2**, the larger cavity than the cavity of receptor **1** seems to be able to accommodate the carboxylate anion and dihydrogen phosphate in 1:1 stoichiometry.

In conclusion, we have synthesized bromide selective fluorescent anion receptor with glycoluril molecular scaffold.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.065.

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6. ^{1}H NMR (DMSO-d_6): 10.1 (s, 4H, CONH), 8.2–7.2 (m, 10H, phenyl) (m, 28H, naphthalene), 4.4 (d, 4H, $J = 16.6$, CH_2CO), 4.0 (d, 4H, $J = 16.6$, CH_2CO); ^{13}C NMR (DMSO-d_6): δ 166.5, 157.9, 135.8, 133.0, 132.0, 129.6, 128.9, 128.1, 128.0, 127.1, 126.9, 126.1, 124.5, 120.1, 115.7, 113.8, 87.7, 44.9; HRMS (FAB) calculated for $C_{64}H_{50}N_8O_6Na$, 1049.3751; found for 049.3751.
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14. The Job plot from ^{1}H NMR also showed 1:1 binding stoichiometry. The plot is available in the supplementary data.